PATENT COOPERATION TREATY



# PCT

## INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

| Applicant's or agent's file reference X-15901 | FOR FURTHER ACTION | See Form PCT/IPEA/416 |
|---|---|---|
| Application No. 031512 | International filing date *(day/month/year)* 24.10.2003 | Priority date *(day/month/year)* 05.11.2002 |
| International Patent Classification (IPC) or national classification and IPC C07K 2/00 | | |
| Applicant AND COMPANY et al. | | |

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 7 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☐ *sent to the applicant and to the International Bureau)* a total of sheets, as follows:
      ☐ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

| | | |
|---|---|---|
| ☒ | Box No. I | Basis of the opinion |
| ☒ | Box No. II | Priority |
| ☒ | Box No. III | Non-establishment of opinion with regard to novelty, inventive step and industrial applicability |
| ☐ | Box No. IV | Lack of unity of invention |
| ☒ | Box No. V | Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement |
| ☐ | Box No. VI | Certain documents cited |
| ☐ | Box No. VII | Certain defects in the international application |
| ☐ | Box No. VIII | Certain observations on the international application |

| Date of submission of the demand | Date of completion of this report |
|---|---|
| 28.04.2004 | 23.02.2005 |
| Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465 | Authorized Officer Usuelli, A Telephone No. +49 89 2399-7366 |

# INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/US 03/31512

## Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:
   - ☐ international search (under Rules 12.3 and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4)
   - ☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

   **Description, Pages**

   1-76 as originally filed

   **Claims, Numbers**

   1-35 as originally filed

   ☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

* *If item 4 applies, some or all of these sheets may be marked "superseded."*

# INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/US 03/31512

## Box No. II Priority

1. ☒ This report has been established as if no priority had been claimed due to the failure to furnish within the prescribed time limit the requested:
   - ☒ copy of the earlier application whose priority has been claimed (Rule 66.7(a)).
   - ☐ translation of the earlier application whose priority has been claimed (Rule 66.7(b)).

2. ☐ This report has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rule 64.1). Thus for the purposes of this report, the international filing date indicated above is considered to be the relevant date.

3. Additional observations, if necessary:

## Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☐ the entire international application,

   ☒ claims Nos. 32-35 (industrial applicability)

   because:

   ☒ the said international application, or the said claims Nos. 32-35 (industrial applicability) relate to the following subject matter which does not require an international preliminary examination (specify):

   **see separate sheet**

   ☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

   ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

   ☐ no international search report has been established for the said claims Nos.

   ☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

   | | | |
   |---|---|---|
   | the written form | ☐ | has not been furnished |
   | | ☐ | does not comply with the standard |
   | the computer readable form | ☐ | has not been furnished |
   | | ☐ | does not comply with the standard |

   ☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

   ☐ See separate sheet for further details

# INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/US 03/31512

**Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement

| | | | |
|---|---|---|---|
| Novelty (N) | Yes: | Claims | 1-35 |
| | No: | Claims | |
| Inventive step (IS) | Yes: | Claims | |
| | No: | Claims | 1-35 |
| Industrial applicability (IA) | Yes: | Claims | 1-31 |
| | No: | Claims | |

2. Citations and explanations (Rule 70.7):

**see separate sheet**

**Re Item III**

**Non-establishment of opinion with regard to novelty, inventive step and industrial applicability**

Claims 32-35 relate to subject matter considered by this Authority to be covered by the provisions of Rule 67.1 (iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject matter of these claims, cf. Article 34(4)(a)(i) PCT.

**Re Item V**

**Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1- Reference is made to the following documents cited in the search report:

d1: EP-373836
d2: US 5023269
d3: Neuropsychopharmacology, 8(1), 23-33, 1993

2- Novelty
Present compounds of formula (I) are novel since they differ from the compounds disclosed in d1 to d3 on account of the group Y.
Since all the claims relate to the compounds of formula (I), the requirements of Art.33.2 PCT are met for all of them.

3- Inventive step
3.1- The applicant has set himself the task of providing novel inhibitors of the serotonin and norepinephrine reuptake which may potentially be used in the treatment of various conditions in particular for the treatment of pain.
Documents d1 to d3 relate to compounds having the same use of present compounds.
D1 is considered to represent the closest state of the art.

For the purpose of assessing the inventive step during the preliminary examination, it is accepted that present compound possess the claimed activity, i.e. that they are indeed inhibitors of the serotonin and norepinephrine reuptake.
The technical problem can therefore be seen in the provision of further serotonin and

norepinephrine reuptake-inhibitors.

3.2- The solution proposed by the present invention, i.e. the compounds of formula (I) do not appear to involve any inventive activity.
The cited documents disclose propanamine derivatives having the same activity of the present compounds and very similar structures.
All the compounds disclosed in these three documents contain a propanamine group substituted in position 3 by a radical corresponding to present group X and by a heteroatom corresponding to present group A to which a group is bound which occupies the same position of the present group Y.
As stated before this group is the sole difference between the compounds of the prior art and the compounds of the invention.
In d1 this group (group R) is a (bicyclic)aromatic or heteroaromatic ring, in d2 (group Ar) and d3 the corresponding radical is a naphthyl or phenyl ring.
In some cases, e.g. when in the present formula (I) Y is quinolyl and R in d1 is naphthyl, the difference between the claimed compounds and the prior art's compounds amount to a single atom. However, the skilled person, would observe that the compounds of d1 to d3 present, in the position corresponding to present group Y, various possible substituents belonging to the broad class of (fused)(hetero)cyclic radicals. From this observation he would deduce that the activity of the propanamine derivatives as serotonin and norepinephrine reuptake-inhibitors, is not affected by the nature of the radical in the position corresponding to present group Y at least insofar this group is a (fused)(hetero)cyclic radical.
Hence, the introduction of a heterocyclic ring in this position is regarded as an obvious modification of the prior art's compounds.

3.3- The fact that the prior art documents neither indicate that the present group R1 is a bioisoster of the corresponding groups of d1 to d3 nor provide information about the impact that the introduction of R1 may have upon the biological activity, does not affect the conclusion that the compounds are not inventive.
In fact, considering that the description does not provide any pharmacological data for individual compounds, the sole reason for accepting that the technical problem of providing further serotonin and norepinephrine reuptake-inhibitors has been successfully solved is the fact that the compounds of formula (I) are structurally so close to the products of d1 to d3 that it appears reasonable to assume that they maintain the same activity.

In this context it is observed that the information that preferred compounds exhibit an IC50 higher than 6 µM fro CYP2D6 (page 74) does not help to decide whether substantially all the claimed compounds have the desired activity as far as it is not which are the preferred compounds tested.

gly, if it is accepted the argument that the skilled person would not be able to the impact of the replacement of the groups of d1 to d3 with present group Y, it lso be concluded that the activity of the present compound cannot be inferred one of the compounds of d1 to d3. The conclusion would be that there is no that the technical problem has been solved. However, compounds which do ve any technical problem cannot be regarded as inventive.